Remarks

Applicants thank the Examiner for the Examiner's careful review of the pending claims and the clarity with which the asserted rejections are set forth.

I. Addressing the Examiner's Rejection of Claims 6, 7, 11-13, 15, 17, 18 and 29 Under 35 U.S.C. §102(e).

The Examiner rejected claims 6, 7, 11-13, 15, 17, 18 and 29 under 35 U.S.C. §102(e) asserting that the claims are anticipated by Bischoff, et al. (U.S. Patent No. 6,080,578).

In the present application, independent claims 11, 12, and 15 are pending. Following herein below, the applicants set forth their arguments that the cited reference does not anticipate the claimed invention at least with respect to the limitations present in the independent claims. Accordingly, the dependent claims define over the cited prior art at least by virtue of their inclusion of the limitations of the independent claims.

1. The reference of Bischoff, et al., does not teach all of the elements of the present invention.

Applicants submit that the reference of Bischoff, et al., does not anticipate the claimed invention. First, it is well established that anticipation under section 102 requires "the presence in a single prior art disclosure of all elements of a claimed invention arranged as in that claim." *Panduit Corp. v. Dennison Manufacturing Co.*, 774 F.2d 1082, 1101, 227 U.S.P.Q. 337, 350 (Fed. Cir. 1985) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548, 220 U.S.P.Q. 193, 198 (Fed. Cir. 1983)). For prior art to anticipate under 35 U.S.C. §102 it has to meet every element of the claimed invention: such a determination is one of fact. *Hybritech Inc. v. Monoclonal Antibodies*, 802 F.2d at 1367, 231 USPQ 81 (Fed. Cir. 1986).

In the present application, the cited references do not teach all of the elements of the present invention. For example, all of the pending independent claims (i.e., claims 11, 12, and 15) contain a limitation relating to preferential killing of dividing endothelial cells compared to quiescent endothelial cells by a replication competent adenovirus, as follows (emphasis added):

> 11. In a cell population comprising dividing and quiescent endothelial cells, **a method for killing said dividing endothelial cells with substantially**

less killing of said quiescent endothelial cells, said method comprising contacting said cell population under infective conditions with a replication competent adenovirus, said adenovirus comprising a mutation in an E1A CR2 RB family member binding region of said adenovirus, and allowing sufficient time for said mutant adenovirus to infect said cell population, wherein said mutant adenovirus replicates to higher titers in said dividing cells than wild type adenovirus.

12. **A method for substantially and selectively killing dividing endothelial cells and cancer cells compared to quiescent endothelial cells** in a cell population comprising said three cell types, **said method comprising contacting said cell population under infective conditions with a replication competent adenovirus** comprising a mutation in an E1A-CR2 RB family member binding region of said adenovirus, and allowing sufficient time for said mutant adenovirus to infect said cell population.

15. A method for controlling angiogenesis in an animal by **substantially and selectively killing dividing microvascular endothelial cells compared to quiescent microvascular endothelial cells**, said method comprising administering to said animal in need of said control a replication competent adenovirus comprising a mutation in an E1A-CR2 RB family member binding region of said adenovirus, and allowing sufficient time for said mutant adenovirus to infect said microvascular endothelial cells.

The reference of Bischoff, et al., does not teach a method of killing dividing endothelial cells with substantially less killing of quiescent cells by contacting the cells under infective conditions with a replication competent adenovirus. The reference of Bischoff, et al., makes no mention of endothelial cells. The reference of Bischoff, et al., makes no mention that replication competent adenovirus can provide preferential killing of dividing endothelial cells relative to killing of quiescent endothelial cells. Further, the reference of Bischoff, et al., provides no teaching concerning mutant adenovirus replicating to higher titers in the dividing endothelial cells than wild type adenovirus (e.g., claim 11).

The reference of Bischoff, et al., teaches "(t)he mutant virus is able to substantially produce a replication phenotype in **neoplastic cells** but is substantially unable to produce a replication phenotype in non-replicating, non-neoplastic cells having essentially normal p53 and/or RB function" (see, e.g., Abstract of Bischoff, et al., emphasis added). Accordingly, the reference of Bischoff, et al., does not teach all of the elements of the claimed invention and cannot be said to anticipate the presently claimed invention.

2. The presently claimed invention is not a natural result flowing from the explicit disclosure of the Bischoff, et al., reference.

The Examiner's arguments asserting anticipation of the presently claimed invention by the teachings of the reference of Bischoff, et al., is essentially an argument that the methods of the present invention relating to preferential killing of dividing endothelial cells relative to killing of quiescent endothelial cells, particularly microvascular endothelial cells, are inherent in the methods of preferential killing of neoplastic cells taught by the reference of Bischoff, et al. In the Office action, the Examiner asserted the following:

> It is noted that patients comprising tumors comprise both dividing cells, such as proliferating cancer cells and proliferating microvascular cells associated with a tumor, as well as non-dividing non-cancerous cells. Therefore, administering the vector taught by Bischoff to a subject having a tumor would necessarily result in substantial and selectively killing dividing endothelial cells (including dividing microvasculature) and cancer cells in the subject. (Office action, dated 12 July 2006, pages 3-4.)

In the absence of the teachings of the present specification, one of ordinary skill in the art would not be guided to use replication competent adenovirus to preferential kill dividing endothelial cells relative to killing of quiescent endothelial cells, which in and of itself provides an art recognized cancer treatment (i.e., disruption of tumor angiogenesis) separable from direct killing of tumor cells (i.e., neoplastic cells) themselves.

In the specification of Bischoff, et al., neoplastic cells are defined as follows:

> As used herein, "neoplastic cells" and "neoplasia" refer to cells which exhibit relatively autonomous growth, so that they exhibit an aberrant growth phenotype characterized by a significant loss of control of cell proliferation. Neoplastic cells comprise cells which may be actively replicating or in a temporary non-replicative resting state (G_1 or G_0); similarly, neoplastic cells may comprise cells which have a well-differentiated phenotype, a poorly-differentiated phenotype, or a mixture of both type of cells. Thus, not all neoplastic cells are necessarily replicating cells at a given timepoint. The set defined as neoplastic cells consists of cells in benign neoplasms and cells in malignant (or frank) neoplasms. Frankly neoplastic cells are frequently referred to as cancer, typically termed carcinoma if originating from cells of endodermal or ectodermal histological origin, or sarcoma if originating from cell types derived from mesoderm. (See, Bischoff, et al., col. 6, lines 40-45.)

The methods of the present invention, however, are directed to preferential killing of dividing endothelial cells relative to killing of quiescent endothelial cells, notably microvascular endothelial cells. The endothelium comprises a single layer of flat cells that line the interior surface of blood vessels. The endothellium forms an interface between

circulating blood in the lumen and the rest of the vessel wall. Endothelial cells are the cells that make up the inside of blood vessels. Angiogenesis is the formation of new blood vessels. Angiogenesis has come to be appreciated as a continuous and important process in tumor development, wherein a tumor may gain an independent blood supply. The process of angiogenesis is believed to be driven by the tumor releasing signals that induce angiogenesis, such as VEGF, by binding to endothelial cell receptors near the tumor (see, e.g., Berse, B., et al., Molec. Cell. Biol. 1992 Feb;3(2):211-20); Warren, R.S., et al., J. Clin. Invest. 1995 Apr;95(4):1789-97). The control of tumor angiogensis has been touted as an alternative method of controlling tumor growth.

In the presently pending claims, claim 12 illustrates a dual approach to cancer treatment, that is, a method for substantially and selectively killing dividing endothelial cells and cancer cells compared to quiescent endothelial cells in a cell population using a replication competent adenovirus. Substantial and selective killing of dividing endothelial cells is useful and can be a separable method from the direct killing of cancer (or neoplastic) cells -- as is illustrate in pending claims 11 and 15 which are directed to preferential killing of dividing endothelial cells and a method for controlling angiogenesis, respectively. Accordingly, applicants submit that there is no guidance in the reference of Bischoff, et al., that would lead one of ordinary skill in the art to a method for killing dividing endothelial cells with substantially less killing of quiescent endothelial cells using infection of the cells with a replication competent adenovirus.

Even, for the sake of argument, in the case of a claimed method comprising steps identical to those of a method practiced in the prior art, and where the same result would have been achieved in the prior art method, the accidental or unwitting achievement of that result cannot be said to constitute anticipation. *In re Marshall*, 578 F.2d 301, 198 USPQ 344 (CCPA 1978). In *In re Marshall*, the claims at issue were directed to a weight control process comprising the administering of an anesthetic (e.g., oxethazaine) "to inhibit said nerve endings from releasing sufficient hormones to cause the release of said pancreatic enzymes which will contact said food as it passes through the digestive tract" (see U.S. Patent No. 4,137,327). The cited reference was the Physician's Desk Reference (1971) pp. 1522-1523 that disclosed use of oxethazaine for treatment of esophagitis, gastritis, peptic ulcer and irritable colon syndrome. The reference disclosed that this anesthetic inhibited

release of the acid-stimulating hormone, gastrin.

The CCPA held that the PDR did not disclose every material element of the claimed subject matter because the claims were directed to a weight control process and nothing in the PDR suggested taking oxethazaine to lose weight. In their decision, the judges opined that "[i]f anyone ever lost weight by following the PDR teachings it was an unrecognized accident." In the present application, the teachings of the Bischoff, et al., reference would lead one of ordinary skill in the art to use mutant adenoviruses having replication phenotype in neoplastic cells for preferential killing of neoplastic cells, either directly or by expression of a cytotoxic gene in neoplastic cells expressing a viral replication phenotype. However, preferential killing of dividing endothelial cells relative to killing of quiescent endothelial cells (as claimed in the present invention) would at most be nothing more than the accidental or unwitting achievement of the presently claimed result by the application of the methods taught by Bischoff, et al., and the reference of Bischoff, et al., should not be said to constitute anticipation.

There is no teaching in the reference of Bischoff, et al., that would guide one of ordinary skill in the art to use the methods of the present invention to achieve the result of the present invention, that is, preferential killing of dividing endothelial cells relative to killing of quiescent endothelial cells. For example, in a situation where a target tumor did not respond to direct killing of neoplastic cells by a selected method (e.g., chemotherapy), in view of the teachings of the present specification one of ordinary skill in the art may choose instead to target the dividing endothelial cells to reduce or eliminate angiogenesis which provides a blood supply to a tumor. The teachings of Bischoff, et al., would not direct one of ordinary skill in the art to such an approach. Accordingly, the reference of Bischoff, et al., should not be said to constitute anticipation.

Further, in general, a limitation or the entire invention is inherent and in the public domain if it is the "natural result flowing from" the explicit disclosure of the prior art. *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970, 58 U.S.P.Q.2d 1865 (Fed. Cir. 2001). In the present case, the invention claimed herein cannot be said to be the natural result flowing from the explicit disclosure of the prior art, as, for example, the cited reference of Bischoff, et al., contains no teachings regarding preferential killing of dividing endothelial cells relative to killing of quiescent endothelial cells. Further, the independent claims of the

present invention are limited to a replication competent adenovirus comprising a mutation in an E1A-CR2 RB family member binding region. Applicants' specification recites, for example, the following regarding mutations specifically in the E1A-CR2 region:

> In another aspect of the invention, replication competent adenoviral mutants that exhibit a mutation in the RB family member binding region of E1A, **preferably the E1A-CR2 region**, are capable of enhanced replication compared to wild type adenovirus in dividing normal or cancer cells. (Specification, page 3, lines 23-26, emphasis added.)

> **The enhanced replication and cytopathogenicity of E1A-CR2 RB binding site mutants versus wild-type adenovirus in proliferating cells was unexpected.** Indeed, several adenovirus and herpes virus mutants are known that have been genetically attenuated in order to achieve selective replication in tumor cells. See, Heise, C. *et al., Nat. Med.* 3, 639-645 (1997); Bischoff, J.R. *et al., Science* 274, 373-376 (1996); Martuza, R.L., *et al., Science* 252, 854-856 (1991); Mineta, T., *Nat Med* 1, 938-943 (1995). Each of these attenuated viruses replicates less efficiently than its wild-type parental virus, even in tumor cells. See, Bischoff, J.R. *et al., Science* 274, 373-376 (1996); Martuza, R.L. *et al., Science* 252, 854-856 (1991); Kirn, D.H., *Expert Opinion on Investigational Drugs* 5, 753-762 (1996). In some cases replication can be reduced by 10 to 100-fold versus the wild-type virus. See, Martuza, R.L. et al., *Science* 252, 854-856 (1991). This is presumably due to the loss of important viral functions that enhance replication. The reason for the enhanced replication of E1A-CR2 RB binding mutants versus wild-type adenovirus is unknown. It will be apparent to the skilled practitioner of this art that the E1A RB binding site mutants disclosed herein, and **preferably the E1A-CR2 RB binding site mutants, have a large therapeutic index between dividing and quiescent cells, or more specifically, tumor and proliferating microvascular endothelial cells, and quiescent microvascular endothelial cells**. (Specification, page 13, line 29, to page 14, line 15, emphasis added.)

These features of the present invention are not a "natural result flowing from the explicit disclosure of the prior art" teachings of the reference of Bischoff, et al. The reference of Bischoff, et al., contains no teaching or suggestion directing one of ordinary skill in the art to specifically use mutations in the E1A-CR2 region of the E1A RB family member binding region for substantial and selective killing of dividing endothelial cells relative to killing of quiescent endothelial cells; in particular, the reference of Bischoff, et al., contains no teaching or suggestion regarding the unexpected and superior properties of mutations in the E1A-CR2 region. For a claim to be inherent in the prior art it "is not sufficient that a person following the disclosure sometimes obtain the result set forth in the [claim]; it must

invariably happen." *Standard Oil Co. v. Montedison, S.p.A.*, 664 F.2d 356, 372, 212 USPQ 327, 341 (3d Cir. 1981). Following the teachings of the reference of Bischoff, et al., that mutations in either the CR1 and/or CR2 domains of E1A, as well as mutations in E1B, are useful in preferential generation of replication phenotype in neoplastic cells resulting in a preferential killing of the neoplastic cells (see, Bischoff, et al., col. 9, line 20, to col. 11, line 20, and the Abstract), **does not invariably** give rise to the methods of applicants' independent claims 11, 12, and 15. Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Accordingly, the reference of Bischoff, et al., cannot be said to inherently anticipate the invention of independent claims 11, 12, and 15 of the present application.

Accordingly, in view of the above arguments, applicants submit that the reference of Bischoff, et al., does not provide teachings that anticipate the presently claimed invention. Applicants respectfully request withdrawal of the rejection of claims 6, 7, 11-13, 15, 17, 18 and 29 under 35 U.S.C. §102(e).

II. Addressing the Examiner's Rejection of Claims 22 and 23 Under 35 U.S.C. §102(b).

The Examiner rejected claim 22 under 35 U.S.C. §102(b) asserting that the claims are anticipated by Whyte, et al. (J. Virol. 1988, previously of record).

The Examiner rejected claim 23 under 35 U.S.C. §102(b) asserting that the claims are anticipated by Jelsma, et al., (Virol. 1989, previously of record).

1. Traversal of rejections.

In the rejection of claim 22, the Examiner asserts the following:

> Whyte teaches several mutant adenoviral vectors including the dl922/947 vector (e.g., see Figure 4) and further teaches that the vectors were administered to cells in tissue culture (e.g., see page 258, column 2) thus indicating that the vectors were in a **physiological solution** (also see page 258, first column). Therefore, Whyte anticipates the instant claim. (Office action, dated 12 July 2006, page 4, emphasis added.)

In the rejection of claim 23, the Examiner asserts the following:

> Jelsma [*sic*] several mutant adenoviral vectors including the dl1107

> vector (e.g., see Figure 1) and further teaches that the vectors were administered to cells in tissue culture (e.g., see Table 2) thus indicating that the vectors were in a **physiological solution** (also see page 121, second column). Therefore, Jelsma anticipates the instant claim. (Office action, dated 12 July 2006, page 4, emphasis added.)

In both references, the teachings referred to by the Examiner appear to relate to administering the adenovirus constructs to BRK cells in culture in order to transfect the BRK cells in culture.

Pending claims 22 and 23 are as follows (emphasis added):

> 22. **A pharmaceutical composition** comprising a Rb binding site adenoviral mutant **in a physiological solution**, wherein said adenoviral mutant is dl922/947.
>
> 23. **A pharmaceutical composition** comprising a Rb binding site adenoviral mutant **in a physiological solution**, wherein said adenoviral mutant is dl1107.

The present specification discusses pharmaceutical compositions, for example, as follows:

> The adenoviral mutants described herein, may be formulated for therapeutic and diagnostic administration to a patient. For therapeutic or prophylactic uses, a sterile composition containing a pharmacologically effective dosage of adenovirus is administered to a human patient or veterinary non-human patient for treatment, for example, of a neoplastic condition. Generally, the composition will comprise about 10^3 to 10^{15} or more adenovirus particles in an aqueous suspension. A pharmaceutically acceptable carrier or excipient is often employed in such sterile compositions. A variety of aqueous solutions can be used, e.g., water, buffered water, 0.4% saline, 0.3% glycine and the like. These solutions are sterile and generally free of particulate matter other than the desired adenoviral vector. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity adjusting agents and the like, for example sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate, etc. Excipients which enhance infection of cells by adenovirus may be included, preferably polycations. (Specification, page 13, lines 7-20.)

Accordingly, pharmaceutical compositions of the present invention generally contain a pharmacologically effective dosage of adenovirus and are free of particulate matter other than the desired adenoviral vector. Further, the pharmaceutical compositions are suitable for administration to a patient.

The physiological solution cited by the Examiner for administration to cells in culture

is a transfection solution. Transfection is typically accomplished using calcium phosphate precipitation, for example, as described in the reference of Whyte, et al., as follows:

> Transfections were carried out by the calcium phosphate precipitation method of Wigler et al. (58). At 24 h after the initial plating of the BRK cells, the medium on the BRK cells was changed, and approximately 4 h later, the cells were transfected with a **calcium phosphate precipitate containing 2 ug of each plasmid being tested plus 8 to 10 ug of sheared salmon sperm DNA as the carrier in a 0.5-ml volume**. The precipitate was left overnight before removal and replacement with fresh medium. Medium was changed every 3 days, and the assay was scored at 3 to 4 weeks after the transfection. Visualization of transformed foci was enhanced before scoring the assay by fixing the cells with methanol and staining with Giemsa stain. (Emphasis added, Whyte, et al., page 259, col. 1.)

Accordingly, such transfection solutions for application to cells in culture are not pharmaceutically acceptable in view of the fact that the transfection solutions include undesirable components for a pharmaceutical composition, for example, non-adenoviral vector carrier DNA (such as, sheared salmon sperm DNA) and levels of calcium phosphate sufficient to cause a precipitate. Further, the physiological solution described by the reference of Whyte, et al., for transfection of cells in culture would not be suitable for administration to a patient in view of its contents (for example, salmon sperm DNA).

The reference of Jelsma, et al., also teaches transfection of BRL cells but the teachings are by reference to two previous publications (i.e., Ruley, H.E. (1983) Nature 304, 602-606; and Graham, F.L. and Bacchetti, S. (1983) Nucleic Acid Biochem. B506, 1-14). Accordingly, applicants respectfully request clarification of the composition of the "physiological solution" taught by Jelsma, et al., as it is likely that it is not a pharmaceutically acceptable solution in view of the typical inclusion in transfection solutions of, for example, carrier DNA (such as, sheared salmon sperm DNA) and levels of calcium phosphate sufficient to cause a precipitate.

In view of the above arguments, applicants submit that the cited references cannot be said to teach all the elements of the present invention. Accordingly, applicant respectfully requests withdrawal of the rejections of the claims under 35 U.S.C. §102(b).

2. Clarification requested regarding second use of references after withdrawal of previous rejection.

Further, the references of Whyte, et al., and Jelsma, et al., were previously used in a rejection of the claims that was subsequently withdrawn, wherein the rejection was also directed to pharmaceutical compositions (see the Office actions dated 15 September 2000, page 10, rejection under 35 U.S.C. §103; Response, 15 March 2001, page pages 5-6; Office action, dated 5 June 2001, pages 4-5; Office action, dated 17 January 2002, pages 4-7, the rejection was not maintained). Further, a similar rejection of the claims was asserted using the references of Yamashita, et al., (Oncogene (1993) 8:2433-2441) and Shisler, et al., (J. Virol., January 1996, pages 68-77) under 35 U.S.C. §102(b) (Office action, 17 January 2002). Applicants set forth their argument in the response dated 17 July 2002, on page 7. The rejections were not maintained in the Office action, dated 20 April 2005 (see pages 6-8).

Clarification concerning why a new rejection is being reasserted based on previously applied references wherein the previous rejections were withdrawn is respectfully requested.

III. Addressing the Examiner's Rejection of Claims 6-13, 15, 17-20, 22, 23, and 26-34 under 35 U.S.C. §112, First Paragraph.

The Examiner rejected claims 6-13, 15, 17-20, 22, 23, and 26-34 under 35 U.S.C. §112, first paragraph, asserting that the specification, "while being enabling for: methods of selectively killing dividing cells in a population of dividing and quiescent cells by administering a replication competent adenovirus comprising a mutation in an E1A CR2 RB family member binding region directly to the target dividing cells, does not reasonably provide enablement for the full scope of the claims." (Office action, dated 12 July 2006, page 5, emphasis in original.)

Applicants submit that the Examiner has failed to establish a *prima facie* case for lack of enablement commensurate in scope with these claims. Applicants' reasoning to support this failure is set forth below. However, first applicants set forth the reasons that the specification provides enablement commensurate in scope with the claimed subject matter.

1. Clarification requested regarding the rejection of claims 22, 23, and 26-28.

Claims 22, 23, and 26-28 are composition claims, not "methods of selectively killing

dividing cells." It is unclear to applicants why the above-recited rejection, which relates to the scope of the method claims, is asserted against the composition claims. Clarification is respectfully requested.

2. Applicants Submit the Specification Provides Enablement Commensurate in Scope with the Claimed Subject Matter.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Ex parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986). A patent may be enabling even though some experimentation is necessary. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217 (Fed. Cir. 1988). Further, a considerable amount of routine experimentation is permissible if the specification provides a reasonable amount of guidance, with respect to the direction in which experimentation should proceed, to enable the determination of how to practice a desired embodiment of the claimed invention. *See, e.g., Ex parte Forman*, 230 USPQ 546, 547 (PTO Bd. Pat. App. & Int'f 1986); *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

Applicants submit that the specification enables one of ordinary skill in the art to use the methods of the present invention relating to substantial and selective killing of dividing endothelial cells compared to quiescent endothelial cells, as well as greater cytopathogenicity relative to wild-type adenovirus of the mutant adenoviruses of the present invention in cancer cells and proliferating endothelial cells, without undue experimentation.

Applicants demonstrated the cytopathic effect (CPE) of adenoviral E1A-CR2 RB family member binding mutants against a number of tumor cell types relative to wild-type adenovirus (see, for example, Example 1, page 16, line 31, to page 17, line 4). Further, applicants demonstrated that the three mutants tested (that is, two deletion mutants each having different deletions in the E1A-CR2 region of adenovirus and one missense mutant having a mutation in the E1A-CR2 region of adenovirus) showed substantial and selective killing of endothelial cells compared to quiescent endothelial cells (see, for example, specification page 17, lines 10-12). Applicants further demonstrated that the adenoviral E1A-CR2 RB family member binding mutants replicated better than wild-type adenovirus in proliferating endothelial cells and in human tumor cells (see, for example, specification page

17, line 22, to page 18, line 10). These data support the present invention as set forth by the applicants:

> Thus, taken together the preferred embodiment of the invention is adenoviral E1A RB family member binding mutants, and more preferred are adenoviral E1A-CR2 RB family member mutants, that are mutated in the RB family member binding region of E1A. These viruses show reduced replication in quiescent normal cells, while replication and cytopathogenicity is greater than wild-type adenovirus in cancer cells and proliferating endothelial cells. (Specification, page 12, lines 10-15.)

In addition, two of the adenoviral E1A-CR2 RB family member binding mutants (one of the deletion mutants and the missense mutant) were used by applicants to demonstrate efficacy against tumors *in vivo* using human tumor xenografts in athymic mice (see, for example, specification page 11, lines 17-26, and page 18, line 11, to page 19, line 14) -- these data support that the phenotypes of applicants' mutants seen *in vitro* correlate to *in vivo* activity. Further, one of the adenoviral E1A-CR2 RB family member binding mutants (a deletion) was used by applicants to demonstrate decreased replication and toxicity *in vivo* in quiescent cotton rat lung cells relative to wild-type adenovirus (see, for example, specification page 11, lines 17-26, and Example 4, page 19, line 15, to page 20, line 7) -- these data also support that the phenotypes of applicants' mutants seen *in vitro* correlate to *in vivo* activity.

In the asserted rejection the Examiner states that "(i)t is noted that intranasal delivery directly delivers the virus to lung tissue cells" (Office action, dated 12 July 2006, page 7). Applicants submit, in view of applicants teachings regarding the efficacy of the methods of the present invention (for example, summarized herein above), that delivery of the virus to the target cells via intranasal delivery supports an intranasal route of administration for the methods of the present invention relating to substantial and selective killing of dividing endothelial cells compared to quiescent endothelial cells.

The Examiner asserted that "(e)xample 4 does not demonstrate that the intranasal administration of the mutant adenoviral vector results in substantially and selectively killing dividing cells without concomitant killing of non-dividing cells" (Office action, dated 12 July 2006, page 7). However, as noted in the specification, the cotton rat is a permissive host for human adenovirus. See, Ginsberg, H.S. et al., Proc Natl Acad Sci U S A 86, 3823-3827 (1989). Its lung is an established model to study adenoviral replication and pathology *in vivo*.

See, Prince, G.A. *et al.*, J Virol 67, 101-111 (1993); Ginsberg, H.S. & Prince, G.A., Infect Agents Dis 3, 1-8 (1994) (see, specification, page 19, lines 18-24.) The ability of the dl922/947 adenoviruses to be delivered to the lung cells via intranasal injection and the relative resistance of quiescent normal cells to dl922/947 versus wild-type adenovirus was confirmed by the data obtained in this example. The methods of the invention are generally related to substantial and selective killing of dividing endothelial cells compared to quiescent endothelial cells. Applicants have demonstrated that adenovirus comprising a mutation in an E1A CR2 RB family member binding region kills dividing endothelial cells with substantially less killing of quiescent endothelial cells (discussed herein above). Further, applicants have demonstrated that delivery of an adenovirus comprising a mutation in an E1A CR2 RB family member binding region (i.e., dl922/947) can to be delivered to the lung cells via intranasal injection wherein the quiescent normal cells are relatively resistant to killing by the adenovirus (see also, Example 6, page 20). The Examiner has not presented any evidence to support the assertion that "(e)xample 4 does not demonstrate that the intranasal administration of the mutant adenoviral vector results in substantially and selectively killing dividing cells without concomitant killing of non-dividing cells" (Office action, dated 12 July 2006, page 7). Although Example 4 does not explicitly teach the killing of dividing cells, it does teach a feature of the invention relevant to the Examiner's scope rejection.

Further, the Examiner has not presented any objective evidence to support an assertion that dividing endothelial cells in the lung would not be susceptible to higher levels of killing by the adenovirus (relative to quiescent endothelial cells) when the adenovirus is delivered via intranasal injection -- particularly in view of the fact that Example 4 demonstrated the delivery of adenovirus to lung cells via intranasal injection. Also, applicants demonstrated in Example 1 (see, specification, pages 16-17) that proliferating small airway epithelial cells (SAECs) were more sensitive to the cytopathic effect (CPE) of the E1A-CR2 RB binding site mutants than to wild-type virus. Accordingly, applicants submit that the Examiner has no basis to question the objective enablement of the present application in regard to intranasal delivery.

Whenever the PTO makes a rejection for failure to teach and/or use the invention, the PTO must explain its reasons for the rejection and support the rejection with (i) acceptable

evidence, or (ii) reasoning which contradicts the applicants' claim: the reasoning must be supported by current literature as a whole and the PTO must prove the disclosure requires undue experimentation. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971).

As discussed herein above, applicants have demonstrated the *in vivo* efficacy of the methods of the present invention using intratumoral injection of adenoviral E1A-CR2 RB family member binding mutants of the present invention. Further, applicants have demonstrated, by use of intranasal inoculation, that the adenoviral E1A-CR2 RB family member binding mutants of the present invention show decreased replication and toxicity in quiescent cotton rat lung cells compared to wild-type adenovirus (see, for example, specification, page 11, line 27, to page 12, line 15, and page 19, line 15, to page 20, line 7). Further, applicants have taught a variety of formulations and methods of administration for the adenoviral E1A-CR2 RB family member binding mutants for use in the methods the present invention (see, for example, specification, pages 13-15).

In addition, applicants have incorporated by reference U. S. Patent No. 5,677,178 in its entirety (see, for example, specification, page 14, lines 19-21, and page 5, lines 4-6). Column 17, lines 1-20, of U. S. Patent No. 5,677,178 states the following:

> A adenovirus suspension containing about 10^3 to 10^{12} or more virion particles per ml may be inhaled as a mist (e.g., for pulmonary delivery to treat bronchogenic carcinoma, small-cell lung carcinoma, non-small cell lung carcinoma, lung adenocarcinoma, or laryngeal cancer) or swabbed directly on a tumor site for treating a tumor (e.g., bronchogenic carcinoma, nasopharyngeal carcinoma, laryngeal carcinoma, cervical carcinoma) or may be administered by infusion (e.g., into the peritoneal cavity for treating ovarian cancer, into the portal vein for treating hepatocarcinoma or liver metastases from other non-hepatic primary tumors) or other suitable route, including direct injection into a tumor mass (e.g., a breast tumor), enema (e.g., colon cancer), or catheter (e.g., bladdercancer).

This teaching of U. S. Patent No. 5,677,178 illustrates a number of suitable routes of administration of adenoviral compositions in addition to intratumoral injection. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Ex parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986). A

patent may be enabling even though some experimentation is necessary. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217 (Fed. Cir. 1988).

Applicants' specification allows one reasonably skilled in the art to "make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." Not every species encompassed by the claims, even in an unpredictable area like the chemical sciences, needs to be disclosed. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). As discussed herein above, two of the adenoviral E1A-CR2 RB family member binding mutants (one of the deletion mutants and the missense mutant) were used by applicants to demonstrate efficacy against tumors *in vivo* using human tumor xenografts in athymic mice (see, for example, specification page 11, lines 17-26, and page 18, line 11, to page 19, line 14) -- these data support that the phenotypes of applicants' mutants seen *in vitro* correlate to *in vivo* activity. Further, one of the adenoviral E1A-CR2 RB family member binding mutants (a deletion) was used by applicants to demonstrate decreased replication and toxicity *in vivo* in quiescent cotton rat lung cells relative to wild-type adenovirus (see, for example, specification page 11, lines 17-26, and page 19, line 15, to page 20, line 7) -- these data directly support the efficacy of multiple routes of delivery.

Finally, even if, for the sake of argument, some further experimentation is necessary for delivery methods for use in the methods of the present invention, so long as the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed, a considerable amount of routine experimentation is permissible. See, e.g., *Ex parte Forman*, 230 USPQ 546, 547 (PTO Bd. Pat. App. & Int'f 1986); *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). As noted above, the present specification and information know in the art describe a variety of routes of administration for administration of adenoviral mutants.

In view of the above amendments and arguments, applicants submit that the claims comply with the requirements of 35 U.S.C. §112, first paragraph. Accordingly, withdrawal of the rejection is respectfully requested.

3. The Examiner Has Failed to Establish a *Prima Facie* Case of Lack of Enablement Commensurate in Scope with the Claimed Subject Matter.

In support of the rejection for lack of enablement commensurate in scope with the claimed subject matter, the Examiner relies in part on a generic discussion of alleged shortcomings of general gene delivery and gene therapy methods (see, for example, Office action, dated 12 July 2006, page 6; Office action, dated 15 September 2000, pages 7-8, Office action, dated 5 June 2001, pages 2-3, Office action, dated 17 January 2002, pages 2-3 "reasons of record," Office action, dated 20 April 2005, pages 2-5 "reasons of record"). This generic discussion is based on two references that present general teachings regarding gene therapy -- that is, Dang, et al., and Eck, et al. The Examiner does not point to any specific teaching in any of these references concerning the use of oncolytic adenoviruses, or adenovirus mutants, as described in the present specification, having greater cytopathogenicity relative to wild-type adenovirus in cancer cells and proliferating endothelial cells, wherein such teaching supports the assertions of the Examiner.

Regarding adenoviral vectors, the Examiner cites Green, et al. (Cancer Gene Therapy, 2002; 9:1036-1042) (see, Office action, dated 12 July 2006, pages 6-7). The reference of Green, et al., is a review article published after the priority date of the present application. The Examiner quotes the reference of Green, et al., as follows:

> The development of a targeted adenoviral vector, which can be delivered systemically, is one of the major challenges facing cancer gene therapy. The virus is readily cleared from the bloodstream, can be neutralised by pre-existing antibodies, and has a permissive cellular tropism. Clinical studies using the ONYX virus have shown limited efficacy, but there are several hurdles to overcome to achieve an effective tumor-specific systemic therapy. In this review, we have summarized the various strategies used to overcome the limitations of adenoviral-mediated gene delivery. (Abstract.)

However, the article is a review of a large number of articles discussing *in vivo* and therapeutic uses of adenovirus. Although the reference states "(c)linical studies using the ONYX virus have shown limited efficacy", efficacy has been demonstrated. Further, many cancer therapies, even traditional, well accepted therapies such as chemotherapy, have "limited efficacy" and are used in combination, for treatment of different types of tumors, used at different stages of the disease or used to treat different aspects of the

disease. Accordingly, the reference of Green, et al., serves to overall support the use of adenoviral vectors for the treatment of cancer therapy, albeit, in some situations, suggesting further improvement (for example, target selectivity). The present invention, however, involves the use the use of conditionally replicating viruses (e.g., adenovirus mutants having greater cytopathogenicity relative to wild-type adenovirus in cancer cells and proliferating endothelial cells). In regard to the use of conditionally replicating viruses, the reference of Green, et al., states the following:

> The use of replicating vectors, which may only infect a small proportion of tumor cells but are designed to allow spread of the virus to neighboring cells, **can significantly increase the efficacy of gene delivery coupled with direct cytolytic activity**. Replication competence can be made conditional on the biology of the cell infected; e.g., key virus proteins can be placed under the regulatory control of cell-specific gene promoters, restricting virus production to the appropriate target cells. This approach is considered in more detail later. A more sophisticated system, however, has been to modify the adenovirus proteins to enable the virus to replicate only in cells that bear cancer-related phenotypes. Two main approaches have been pursued, and these are considered briefly here. (Emphasis added, Green, et al., page 1038, col. 2.)

The reference of Green, et al., goes on to discuss the two main approaches for use of conditionally replicating viruses, such viruses typically have mutations in the E1A and E1B regions of adenovirus. As noted above, the claimed methods of the present invention employ adenovirus comprising a mutation in an E1A CR2 RB family member binding region.

The Examiner goes on to discuss particular clinical trials for which the data was published in 1999, 2000 and 2001, as follows:

> In the clinical trials using ONYX-015, the majority of patients presented with neutralizing antibodies and almost all showed a significant increase in liter after the initial virus injection. There are also significant concerns over vector immunogenicity following the death of a patient after hepatic artery infusion of a replication-defective Ad5 vector. It is thought that viral capsid proteins are involved in the acute cytokine release observed shortly after virus administration. (Green, et al., page 1039, col. 2.)

However, the following paragraph in the reference of Green, et al., goes on to discuss more recent trials in which systemic administration of adenovirus was shown to

be well tolerated and resulted in metastatic infection of pulmonary tumors. The data suggested the feasibility of systemic delivery of conditionally replicating adenovirus for treatment of tumors. For example, the reference of Green, et al., states the following:

> The only clinical trials to date involving systemic delivery of conditionally replicating viruses are the ONYX-015 studies. The virus has been administered by hepatic artery infusion for the treatment of metastatic colorectal cancer and intravenously in patients with metastatic lung tumors. Both studies were dose escalation regimens. No dose-limiting toxicity was identified, and the toxicity profile was not altered when the virus was coadministered with chemotherapy. The most common side effects were mild to moderate fever, rigors, and a dose-dependent transient transaminitis. Neutralizing antibody titers were significantly increased. Evidence of viral replication in the blood was detectable in patients receiving virus doses >2 x 10^{11} particles and i.t. replication was confirmed in one patient in the intravenous delivery trial. No objective tumor responses were demonstrated with ONYX-015 alone, but a partial response and tumor stabilization were observed in patients who had been treated with high doses of ONYX-015 and chemo therapy. **These studies have demonstrated that intravascular infusion of ONYX-015 was well tolerated and resulted in viral infection of metastatic pulmonary tumors and i.t. viral replication, suggesting that systemic delivery of genetically modified adenoviral vectors is a feasible approach.** (Emphasis added, Green, et al., page 1040, col. 2.)

Accordingly, applicants submit that the reference of Green, et al., overall supports enablement of the present invention in regard to the use of multiple routes of delivery of adenoviral vectors beyond the scope limitation suggested by the Examiner in the rejection, that is, "administering a replication competent adenovirus comprising a mutation in an E1A CR2 RB family member binding region directly to the target dividing cells" (Office action, dated 12 July 2006, page 5, emphasis in original).

Not every species encompassed by the claims, even in an unpredictable area like the chemical sciences, needs to be disclosed. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Even if, for the sake of argument, some further experimentation is necessary for different routes of administration for use in the methods of the present invention, so long as the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed, a considerable amount of routine experimentation is permissible. See, e.g., *Ex parte Forman*, 230 USPQ 546, 547 (PTO Bd. Pat. App. & Int'f 1986); *In re Wands*, 858 F.2d 731, 8

USPQ2d 1400 (Fed. Cir. 1988). The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Ex parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986). A patent may be enabling even though some experimentation is necessary. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217 (Fed. Cir. 1988).

Even, for the sake of argument, if the experimentation is complex, MPEP 2164.01 (Eighth Edition), states:

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

In addition, applicants have previously discussed (see, for example, Response to Final Rejection and Amendment, dated 20 June 2005, page 10) specific references in the field of oncolytic adenoviruses that provide discussion of routes of delivery for adenoviral vectors. In addition to these references, the issued U.S. Patent literature comprises several examples of issued claims to oncolytic adenoviral vectors wherein the claims embrace *in vivo* uses and routes of administration in addition to direct intratumoral delivery. For example, U.S. Patent No. 5,677,178 contains the following issued method claims (emphasis added):

> 1. A method for ablating neoplastic cells in a cell population, comprising the steps of: contacting under infective conditions (1) a recombinant replication deficient adenovirus lacking an expressed viral oncoprotein capable of binding a functional p53 tumor suppressor gene product, with (2) a cell population comprising non-neoplastic cells containing said functional p53 tumor suppressor gene product which forms a bound complex with a viral oncoprotein and neoplastic cells lacking said functional p53 tumor suppressor gene product, thereby generating an infected cell population.
> 8. A method according to claim 1, wherein said cell population comprising neoplastic cells and non-neoplastic cells is present in a mammal and **said contacting step is performed in vivo by administering the recombinant replication deficient adenovirus to a mammal.**
> 9. A method according to claim 8, wherein the mammal is a human.

The specification of U.S. Patent No. 5,677,178 describes the following routes of administration:

> Suspensions of infectious adenovirus particles may be applied to neoplastic tissue by various routes, including intravenous, intraperitoneal, intramuscular,

> subdermal, and topical. A adenovirus suspension containing about 10.sup.3 to 10.sup.12 or more virion particles per ml may be inhaled as a mist (e.g., for pulmonary delivery to treat bronchogenic carcinoma, small-cell lung carcinoma, non-small cell lung carcinoma, lung adenocarcinoma, or laryngeal cancer) or swabbed directly on a tumor site for treating a tumor (e.g., bronchogenic carcinoma, nasopharyngeal carcinoma, laryngeal carcinoma, cervical carcinoma) or may be administered by infusion (e.g., into the peritoneal cavity for treating ovarian cancer, into the portal vein for treating hepatocarcinoma or liver metastases from other non-hepatic primary tumors) or other suitable route, including direct injection into a tumor mass (e.g., a breast tumor), enema (e.g., colon cancer), or catheter (e.g., bladder cancer). (U.S. Patent No. 5,677,178, col. 16, line 65, to col. 17, line 14.)

The present specification describes a variety of routes of administration for the methods of the present invention (see, discussion of enablement herein above) including reference to U.S. Patent No. 5,677,178 (see, for example, specification page 14, lines 20-21).

Further U.S. Patents having claims to methods of treatment using adenoviral vectors, wherein the vectors are not limited to direct administration in the method of treatment, for example: 5,801,029; 5,846,945; 5,856,181; 6,296,845; 7,001,596; and 7,078,030. These patents typically discuss various routes of administration including, but not limited to, intravenous, intraperitoneal, intramuscular, subdermal, topical, inhalation, infusion, and direct administration.

Whenever the PTO makes such a rejection for failure to teach and/or use the invention, the PTO must explain its reasons for the rejection and support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts the applicants' claim: the reasoning must be supported by current literature as a whole and the PTO must prove the disclosure requires undue experimentation. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971). In view of the above-recited teachings of the literature with regard to oncolytic adenoviruses, their killing properties, and routes of administration, the "current literature as a whole" cannot be said to support the Examiner's allegations of a lack of enablement for the scope of the claimed invention.

In view of the above arguments, applicants submit that the Examiner has failed to establish a *prima facie* case for lack of enablement and undue experimentation. Accordingly, withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph, is respectfully requested.

IV. Supplemental Information Disclosure Statement.

Accompanying this response is a Supplemental Information Disclosure Statement listing seven U.S. Patents and two non-U.S. Patent publications. A Form 1449 listing the references and copies of the cited, non-U.S. Patent publications accompany this paper. Applicants request that the Examiner indicate that the references have been considered by initialing each cited reference on the accompanying modified form 1449 and by returning a copy of the initialed form to the applicants.

Conclusion

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please direct all further communications in this application to:

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If the Examiner notes any further matters that the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact Gregory Giotta at (510) 597-6502.

Respectfully submitted,

Date: 13 Nov 2006

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